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EXAMINER	
KIM, JENNIFER M	
ART UNIT	PAPER NUMBER
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,765	LIPSKY, RICHARD	
	Examiner	Art Unit	
	JENNIFER M. KIM	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 32-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 27, 2008 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(New Matter Rejection)

Claims 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, Applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that application was in possession of the claimed invention.

Instant specification on page 7 [0030] disclose that "naloxone may be administered at a **rate** of **1.4mg/kg/hr** without exposing to the patent to unnecessary risks". However, "a **single dosage of naloxone, wherein an amount of said naloxone is based on said patient's weight and is 1.4mg/kg"** lack literal support in the specification as originally filed.

The premise for the limitation of "a **single dosage of naloxone, wherein an amount of said naloxone is based on said patient's weight and is 1.4mg/kg**" appears to be derived from the observation in the instant specification that on page 7 [0030] discloses that "naloxone may be administered at a **rate** of 1.4mg/kg**/hr** without exposing to the patient to unnecessary risks". The specification does not however, indicate why one should assume based on this disclosure of a **particular administration rate (mg per kg per hour)** that naloxone is administered as **a single dosage based on patient's weight**, i.e. **1.4mg/kg**. Further, the limitation of 39 "wherein said amount is 50mg", depends from claim 38 drawn to "an amount of said naloxone is based on patient's weight and is 1.4mg/kg. This also lack literal support in the specification as originally filed.

This is a **new matter rejection**.

(Enablement Rejection)

1. Claims 1, 4 and 32-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "method for opiate detoxification comprising administering to **a 70kg patient by injection a single 50mg dose of naloxone**", does not reasonably provide enablement for the "method for opiate detoxification comprising administering to **a patient by injection a single 50mg dose of naloxone**". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

2. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method for opiate detoxification comprising administering to a patient by **injection a single 50mg dose of naloxone**. The nature of the invention is extremely complex in that it encompasses the actual administration of a single 50mg naloxone injection

to a patient for opiate detoxification such that the subject treated with above dosage amount in a single injection detoxify opiate compounds.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass administration of a single 50mg naloxone injection in humans which has potentially many different toxic effects (i.e. many different adverse effects or combination of adverse effects). Each of which may or may not be addressed by the administration of the claimed amount in a single injection of naloxone.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed single injection of the specified amount to a subject in order to actually performing an opiate detoxification is minimal. All of the guidance provided by the specification is directed towards a specific patient population, i.e. a 70kg patient, rather than "a patient".

Working Examples: All of the working examples provided by the specification are directed toward the specific patient population (i.e. a 70kg patient) rather than any patient population.

State of the Art: While the state of the art is relatively high with regard to detoxification of opiate comprising adminsitering opioid antagonist, (i.e. naloxone) to a **specific patient population based on patient's specific weight**, the state of the art with regard to administration of a single injection dose of 50mg to any population is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to

the claimed compounds was administered in a single 50mg injection to any population for opiate detoxification.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual administration of a single 50mg injection dose in any human subject including pediatric population, geriatric population with the claimed compound makes practicing the claimed invention unpredictable in terms of administration of a single 50mg injection dose in any human subject population.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage in a single injection, and appropriate animal model system for the claimed compound and test the combination in the model system to determine whether or not the combination is effective for opiate detoxification for any subject population. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to opioid detoxification comprising administration of a single 50mg injection to any subject population, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound singe injectable dosages, patient population, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding opiate

detoxification comprising administering to a patient a single 50mg injection of naloxone to **any subject population**, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to detoxify opiate comprising administering to a patient by injection a single 50mg dose of naloxone.

Therefore, a method for opiate detoxification comprising administering **to a patient** by injection a single 50mg dose of naloxone is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fink (1972) of record in view of McDonald et al. (April 2001) of record.

Fink teaches that naloxone can be administered in a daily oral dosage of **200mg** provided effective blockade to heroin. Fink also teaches that naloxone can be given in a **single oral dosages** increased to 3.0 gram.

Fink does not teach 50mg of naloxone administered based on patients weight as 1.4mg/kg.

McDonald et al. teach that opioids detoxification was produced by infusion of 25mg naloxone for 30 minutes, Followed by a 24 hour infusion of 1 mg per hour. (abstract). Therefore, McDonald et al's a daily (24 hour period) naloxone is 50mg. Accordingly, McDonald et al's daily dosage of naloxone in mg/kg is 1mg/kg.

It would have been obvious to one of ordinary skill in the art to adjust the oral dosage of naloxone to 50mg single dosage because McDonald et al. teach that 50mg daily dosage is effective for the providing opioid detoxification and because Fink teaches that naloxone can be given in a single oral dosages up to 3 gm. Further, the specific safe and effective amount will be vary, with such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of the concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the formula therein and the dosage regimen desired for the composition. The determination of amounts which the active ingredients is

based on certain factor (e.g. patients weight) does not alter the fact that naloxone has been previously administered in the same daily amounts (50mg) as claimed. The patient, the total daily amount, condition to be treated and the effect are the same. An explanation of how the amount may have determined by the patient's weight does not make novel or even unobvious the treatment of the conditions encompassed by the claims.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et al. (April 2001) of record in view of Fink (1972) of record.

McDonald et al. teach that opioids detoxification was produced by infusion of 25mg naloxone for 30 minutes, Followed by a 24 hour infusion of 1 mg per hour. (abstract). Therefore, McDonald et al's a daily (24 hour period) naloxone is 50mg.

McDonald et al. do not teach the administration of 50mg naloxone in a single dosage by injection.

Fink teaches that naloxone can be given in acute single intravenous doses. (page 174, right-hand side, first full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naloxone in daily dose of 50mg taught by McDonald et al. in a single dose for the treatment of opiate addiction or detoxification because Fink teaches that the naloxone can be administered in acute single intravenous doses and because daily dose of 50mg is effective in opioid detoxification as taught by McDonald et al. One would have been motivated to make such a modification in order to

successfully treat opiate detoxification in a single convenient intravenous dose of naloxone in view of Fink. There is a reasonable expectation of successfully treating opiate detoxification with 50mg single dosage of naloxone because the effectiveness of 50mg daily dosage administration of naloxone in treatment of opioids detoxification is well taught by McDonald et al. and the effects of naloxone given in acute single intravenous disease is well taught by Fink.

Claims 4, 32-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et al. (April 2001) in view of Fink and further in view of Legarda Ibanez (U.S.Patent No. 6,103,734), Takrouri et al. (2002), Gooberman et al. (U.S.Patent No. 5,789,411), all of record.

McDonald et al. teach that opioids detoxification was produced by infusion of 25mg naloxone for 30 minutes, followed by a 24 hour infusion of 1 mg per hour. (abstract). Therefore, McDonald et al's a daily (24 hour period) naloxone is 50mg. Accordingly, McDonald et al's daily dosage of naloxone in mg/kg is 1mg/kg.

McDonald does not teach the administration of dextromedetomidine (PRECEDEX) and the rate of administration and detoxification process comprising anesthetizing, intubating, stabilizing the patient, giving Valium, Xanax, Trazodone, antiemetics and antiperistaltic agents, administration of antihistamine agent prior to administering opioids antagonist and further administering nalmefene (REVEX).

Legarda Ibanez teaches a method to suppress opiates dependence with combination of chemical compounds used as a medicament comprising administering

antiemetic, sedating or anesthetizing agent, H2-antihistamine, benzodiazepine and alpha-adrenergic agent such as clonidine. (claims 1-13). Legarda Ibanez teaches that an alpha-adrenergic agonist such as clonidine increases sedation and diminishes the symptomatology of the syndrome of opiate abstinence. (column 2, lines 39-42). Legarda Ibanez teaches the combination of chemical compounds in opiate dependence treatment allows an ultra rapid approach for the detoxification of polydrug users who are addicted to heroin and/or Methadone or other opiates. (column 3, lines 12-15).

Takrouri et al. teach that dexmedetomidine (Precedex) is a potent new alpha-2 adrenoreceptor agonist more than 7 times of alpha –2 activity than clonidine. Takrouri et al. teach that dexmedetomidine has potent sedative, analgesic and sympatholytic effects blunt the cardiovascular responses without unexpected toxicity. (abstract).

Gooberman et al. teach that rapid opioids detoxification procedure with naloxone comprising sedating a patient with an anesthetic agent comprising administering a diarrhea suppressant agent, neuromuscular blocking agent. (abstract, claims). Gooberman et al. also teaches that nalmefene (Revex) can be administered to the patient after the initiation of the withdraw with naloxone. (column 5, lines 34-37).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the opioids detoxification method taught by McDonald and employ combination of chemical compounds such as antiemetic, sedating or anesthetizing agent, H2-antihistamine, benzodiazepine and alpha-adrenergic agent taught by Legarda Ibanez because Legarda Ibanez teaches that the combination of chemical compound with naloxone detoxification allows an ultra rapid approach for the

detoxification of polydrug users who are addicted to heroin and/or Methadone or other opiates. With regard to the employment of Precedex (dexmedetomidine) and nalmefene (Revex) as well as the specific benzodiazepine (e.g. Valium, Xanax) are all deemed obvious because the usefulness of the active agents in combination with naloxone in opioids detoxification has been collectively taught by the combined teachings of the references. It would have been obvious to one of ordinary skill in the art to further modify the method of Legarda Ibanez and replace clonidine with dexmedetomide as an alpha adrenergic agonist in view of Takrouri et al. who teach that dexmedetomidine is more potent than clonidine in treating sedation without toxicity. It would have been obvious to one of ordinary skill in the art to further incorporate Revex in opioids detoxification comprising naloxone as modified by Legarda Ibanez because the administration of nalmefene (Revex) to a patient after the initiation of the withdraw process with naloxone is well known in view of Gooberman et al. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Response to Arguments

Applicant's arguments filed June 27, 2008 have been fully considered but they are not persuasive. Applicant argues that one skilled in the art would not have thought it obvious, regardless of the teachings of the cumulative art, to administer such high dosages of naloxone, especially in a single bolus injection. This is not found to be persuasive because McDonald et al. teach that naloxone can be administered in daily dosage of 50mg infusion and the oral single dosages of naloxone can be administered up to 3 gram. The oral single dosage administered by Fink is 60 times the dosage of the parenteral dosages taught by McDonald et al. Therefore, one of ordinary skill in the art would recognize that single injection of naloxone in 50mg daily parenteral administration including injection dose would be reasonable in view of 3 gm single dose and 50mg daily infusion dosage taught by the cited references. Applicant argues that an injection is not same as an infusion and the table in Applicant's response show that the infusion rates of McDonald are 0.83mg/min for the initial naloxone dose and significantly less, 0.01667mg/min, for each of the supplemental dose. This is not persuasive because the determination of which the active ingredients infused over at certain rate does not alter the fact that naloxone has been previously administered in the same daily amounts as claimed. The patient, the total daily amount, condition to be treated and the effect are the same. An explanation of how the amount may have determined by the patient's weight does not make novel or even unobvious the treatment of the conditions encompassed by the claims.

It is suggested, to advance the prosecution of the subject application, that a side by side comparison of stability be performed and results submitted per Rule 1.132 for review by the Patent Office. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER M KIM/
Primary Examiner, Art Unit 1617

Jmk
September 18, 2008